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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,061	10/06/2000	Stephen H. Bartelmez	0450-0031.30	2847

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/684,061	Bartelmez et al
Examiner	Art Unit
First Last JANE ZORA	1234 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-17, 19, and 20* is/are rejected.

7) ☒ Claim(s) *18* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed October 15, 2002, Paper Nos. 15 and 16.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 15, 2002 has been entered.

Claims 1-20 are pending in the instant application.

Response to Arguments and Amendment

The declaration filed October 15, 2002, Paper No. 16, has been entered and considered but does not overcome the rejection for the reasons set forth in 35 U.S.C. 112, first paragraph rejections below.

Withdrawn Rejections

Rejection of claims 5 and 14 under 35 U.S.C. 112, second paragraph, is hereby withdrawn in light of Applicants' amendments filed October 15, 2002, Paper No. 16.

Rejection of claims 1-16 and 20 under 35 U.S.C. 112, first paragraph, for lacking enablement over the broad scope claimed, is hereby withdrawn in light of Applicants' amendments filed October 15, 2002, Paper No. 16.

Rejection of claims 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Mitani et al in view of Baracchini et al, is hereby withdrawn in light of Applicants' amendments and remarks filed October 15, 2002, Paper No. 16.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially uncharged backbone" in claim 19, lines 1 and 2, is vague and unclear. Clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods for modulating hematopoietic stem cell differentiation comprising the administration of antisense oligonucleotides that target and sequences spanning the translational start codon or intron/exon junction site of any mRNA preferentially expressed in stem cells.

The specification and claims do not teach or adequately describe the members of the broad genus drawn to sequences spanning the translational start codon or intron/exon junction site of any mRNA preferentially expressed in stem cells. No structural attributes identify the members of the genus comprising sequences spanning intron/exon junction sites of mRNA preferentially expressed in stem cells. Furthermore, the genus comprising mRNA preferentially expressed in stem is very broad, and inadequate guidance has been provided in the instant disclosure for identifying members of the genus from others. The general knowledge and level of skill int he art do not supplement the omitted description because specific, not general, guidance is what is needed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the broad genus comprising any and/or all mRNA preferentially expressed in stem cells, and one of skill in the art would reasonably conclude that the disclosure fails to provide adequate description of sequences comprising the intron/exon junction sites of any and/or all mRNA preferentially expressed in stem cells. Thus, Applicant was not in possession of the claimed genus.

Claims 1-16 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for decreasing the number of high proliferative potential colony

forming cells (HPP-CFC) following in vitro administration of an antisense oligonucleotide which targets the zinc finger protein EVI-1 , does not reasonably provide enablement for a method of modulating hematopoietic stem cell differentiation in vivo, in vitro or ex vivo comprising the administration of antisense which target any and/or all mRNA preferentially expressed in stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for the modulation of hematopoietic stem cell differentiation in vitro, in vivo or ex vivo comprising the administration of any and/or all morpholino containing antisense oligonucleotides which target the translational start codon or any intron/exon junction site of any and/or all mRNA that is preferentially expressed in any stem cells.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene delivery in organisms. Branch and Crooke teach that the *in vivo* (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was

illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using various vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Advances have been made regarding regulating hematopoietic stem cell differentiation, with advances being made in vitro manipulation of stem cells (See Thiede et al, Bachovian et al, and Quesenberry in their entirety). The examples provided in the declaration filed on October 15, 2002 (Paper No. 15) also provide concrete examples of antisense inhibition of various target genes in various in vivo systems. But the ability to extrapolate in vivo success from in vitro results is highly unpredictable, and the ability to modulate hematopoietic stem cell differentiation using antisense, either by in vivo administration, or by infusion of in vitro transfected cells (i.e. ex vivo) is a highly unpredictable endeavor.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of modulating hematopoietic stem cell differentiation using antisense which target any and/or all mRNA that is preferentially expressed in stem cells, either by in vivo administration, or by infusion of in vitro transfected cells. The specification teaches the administration in vitro of SEQ ID NO: 1 to isolated murine hematopoietic stem cells whereby an

alteration of phenotype is observed in the target cells. The specification fails to teach the modulation of hematopoietic stem cell differentiation of any patients comprising the administration of antisense which target and inhibit the expression of any and/or all mRNA which is preferentially expressed in stem cells. One skilled in the art would not accept on its face the examples given in the specification of in vitro transfection into hematopoietic stem cell isolates of SEQ ID NO: 1, which targets the mRNA encoding Evi-1 zinc finger protein as being correlative or representative of the successful inhibition of cellular proliferation or increasing the number of lineage committed progenitor cells and their progeny in vivo comprising the administration of antisense oligonucleotides which target any and/or all mRNA preferentially expressed in stem cells in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the efficacy of antisense in reaching and entering the appropriate target cell in vivo and subsequently inhibiting cellular proliferation of or altering the phenotype of target cells, or increasing the number of lineage committed progenitor cells in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo or ex vivo delivery and modulation of hematopoietic stem cell differentiation provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for modulating hematopoietic stem cell differentiation comprising the administration in vivo, or the

infusion of an antisense treated stem cell containing population of cells following ex vivo transfection, of one or more antisense oligomers which are directed to any mRNA which is preferentially expressed in stem cells, whereby an increase in the number of lineage committed progenitor cells and their progeny in the peripheral circulation is observed in the patient. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring all target genes of the genus comprising any and/or all genes which are preferentially expressed in stem cells, and further that hematopoietic stem cell differentiation is modulated. Since the specification fails to provide any particular guidance for the identification of all mRNA which is preferentially expressed in stem cells, nor the nucleotide sequences encoding their translation codon or intron/exon junction sites, as well as failing to provide inhibition of their expression whereby hematopoietic stem cell differentiation has been modulated in an organism, or whereby an increase in the number of lineage committed progenitor cells has been obtained in an organism, and since determination of these factors for a particular antisense targeting a particular gene which is preferentially expressed in stem cells is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Soreq et al in view of Baracchini et al.

The claim is drawn to morpholino containing antisense oligonucleotides that target the translational start codon of a gene preferentially expressed in stem cells.

Soreq et al (WO 93/21202, provided in the Supplementary IDS filed March 26, 2002, Paper No. 11) teach compositions comprising antisense oligonucleotides that target a sequence spanning the translational start codon of a gene preferentially expressed in stem cells (See the abstract, pages 26-27, claims 1, 7 and 8).

Soreq et al do not teach morpholino containing antisense oligonucleotides.

Baracchini et al (USPN 5,801,154) teach the morpholino containing antisense oligonucleotides with substantially uncharged backbones (See especially col. 6).

It would have been obvious to one of ordinary skill to utilize antisense oligonucleotides to target the translational start codon of a mRNA that has been found to be preferentially expressed in stem cells, as taught previously by Soreq et al. One of ordinary skill in the art would have been motivated to target previously identified genes that are preferentially expressed in stem cells in order to study the genes' role(s) in the process of stem cell differentiation. It would have been obvious to one of ordinary skill in the art to incorporate morpholino groups into antisense oligonucleotides because such modifications had been successfully incorporated into antisense oligonucleotides, as taught previously by Baracchini et al, and morpholino containing oligonucleotides were well known at the time of the invention to provide nuclease resistance and enhance targeting and cellular uptake. Therefore the invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claims 18 and 19 are free of the prior art searched, ***as they pertain to elected SEQ ID NO: 1.***

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

December 28, 2002

KAREN LACOURCIERE
PATENT EXAMINER

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